

REMARKS

§102(e) Rejection

Claims 1-3 and 5-9 were rejected under 35 U.S.C. §102(e) as being unpatentable over Kim *et al*, U.S. Patent No. 5,648,225 ("Kim"). (Paper no. 22, para. 5). This citation and the particular grounds for rejection has not heretofore been raised. For the reasons presented below, however, reconsideration and withdrawal of the rejection respectfully is solicited.

Kim discloses a multipurpose reagent system for rapid analysis of a whole blood sample allowing the determination of five classes of peripheral white blood cells, nucleated red blood cells, and lymphocyte immunophenotyping on automated hematology instrumentation. (Abstract). The system includes a non-quartenary ammonium salt, an aliphatic aldehyde having one to four carbons, a non-phosphate buffer substantially inert to the aliphatic aldehyde, and water. (Column 3, lines 47-51). Optional reagents include a surface active agent such as saponin, an anticoagulant, an alkali salt of bicarbonate, a nuclear stain *or* an antibody directed against specific cell surface antigens. (Column 3, lines 52-56, emphasis added).

Anticipation under §102 requires "identity of invention." *Glaverbel Societ Anonyme v. Northlake Mktg. & Supply.*, 33 USPQ2d 1496, 1498 (Fed. Cir. 1995). Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim. *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978); *Lindeman Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 221 USPQ 481, 485 (Fed. Cir. 1984). There must be no differences between what is claimed and what is disclosed in the applied reference. *In re Kalm*, 154 USPQ 10, 12 (CCPA 1967); *Scripps v. Genetech Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991).

Kim fails to disclose use of a nucleotide fluorescent dye and a fluorescent leukocyte binding antibody in the same method or process. Thus, the two particular method steps of staining as claimed by Applicant in claim 1 are absent from Kim. As such Kim fails to teach, suggest or disclose all elements of the claims under rejection. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

§103(a) Rejection

Claims 4 and 10-13 were rejected under 35 U.S.C. §103(a) as being unpatentable over Kim and Inami et al., U.S. Patent No. 5,298,426 ("Inami"). (Paper no. 22, para. 6). For the reasons presented below, however, reconsideration and withdrawal of the rejection respectfully is solicited.

In making the instant rejection, the Examiner relied on Kim, as discussed previously with respect to the rejection under §102(e). The Examiner acknowledged, however, that Kim failed to disclose permeabilizing cell membranes by incorporating reagents and buffers at specific pH and osmolarity parameters in a two step method.” (Paper 22, para.6)

To fill the acknowledged gap, the Examiner relied on Inami for “disclosing” “mixing blood with a hypotonic fluorescent dye solution capable of diffusing into erythroblasts to stain their nuclei and a buffer for maintaining pH in the acidic range.” (Paper 22, para. 6). The Examiner further relied on Inami for “disclosing” mixing the (acidic) sample mixture with a second fluid comprising a buffer that neutralizes the acidic pH in the solution to a value at which the shape and integrity of the leukocytes are maintained.” (Paper 22, para. 6).

The Examiner then contended that it would have been obvious to combine the teachings of Kim and Inami because, according to the Examiner:

“Kim specifically taught that integrity and antigenicity of white blood cells need to be maintained optimally during permeabilization, i.e. lysing, of the nRBC’s or erythroblasts so as to allow accurate simultaneous quantitation of both populations, sometimes requiring quenching of lytic activity of the reagent because of its damaging effect to leukocytic populations and Inami specifically taught that such a procedure eliminates such extreme lysing conditions for erythroblasts while maintaining the integrity and shape of WBCs for accurate differentiation of both erythroblast and leukocyte populations” (Paper 22, para.6).

The deficiencies in the Examiner’s §103 rejection are plain. Applicant has already demonstrated that Kim does not teach simultaneous analysis of a sample using 1) erythroblast nucleotide dye staining and 2) leukocyte cell surface marker fluorescent labeling, as in Applicant’s Claim 1, from which Claim 4 and 10-13 ultimately depend. Since it does not teach such simultaneous analysis, Kim also does not teach analysis of the two signals, i.e. nucleotide fluorescent signal and fluorescent labeled antibody signal which is recited in Applicant’s Claims. In addition, the Examiner also specifically acknowledges that “Kim and Inami are silent in disclosing differentiating between different stages of erythroblast populations,” as recited in Claim 10, and as is incorporated, by their dependency on Claim 10, into Claims 11 and 12.

Given the absence of these elements and limitations, the Examiner has not accounted for all elements and limitations of Applicants’ claims. Fundamental to a rejection under §103 obviousness, is that the cited references account for *all* claimed elements and limitations. *In re Royka*, 180 USPQ 580 (CCPA 1974). Furthermore, it is also fundamental that, to reject claims to a method, the references relied upon by the Examiner must account for the manipulative steps claimed. *In re Magat*, 112 USPQ 317, 319 (CCPA 1957). It is simply not sufficient to only account for all material and structural limitations which may also be present in

a method claim without accounting for the affirmative active steps claimed that act upon, in, or with them. In this regard, Kim and Inami both fail to account for all the steps claimed by Applicant.

Neither Kim nor Inami, moreover, disclose the affirmative manipulative steps taken with respect to the two signal types, i.e. nucleotide fluorescent and fluorescent labeled antibody signals, appearing in Applicants' claims. While the Examiner contends that these gaps are filled by the references taken in combination, combining the references does not fill the gap as to how these two signals may be acted upon together according to Applicants' method claims. Therefore, at the very least, the Applicants claimed steps of *detecting*, *analyzing*, and *discriminating between* these two signals, are necessarily absent and the Examiner's rejection improperly fails to account for them.

In contrast, the standard is clear that "all words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970). Clearly, the words of the manipulative steps embodied in Applicants' method claims have not been properly considered. The rejection therefore fails.

In addition to the lack of disclosure in the cited references accounting for Applicants' claimed manipulative steps, the rejection also lacks the necessary demonstration of a motivation to combine the references. For instance, the Examiner states that it would have been obvious to combine Inami with the reagent system of Kim because the specific pH and osmolarity disclosed in Inami maintain the integrity of white blood cells, which Kim assertedly teaches. Yet, the Examiner states that Kim already has its own concentration of other compounds, such as aldehydes, non-quartenary mono-ammonium salts and buffer to maintain the integrity of white blood cells. (Paper 22, para. 5). The Examiner fails to reveal any

motivation, suggestion or teaching for replacing the components already present within Kim with the nucleotide fluorescent dyes of Inami, even without enumerating the particular ranges; nor does the Examiner provide any basis for believing such substitution in the reagent system of Kim would be successful. Rather, it appears just as feasible that the Examiner's manipulation of the reagent of Kim would be redundant: a fifth wheel. This is not evidence of motivation to combine Kim and Inami to reach the steps recited by Applicant's claims.

"The mere fact the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP §2143.01 (2000 Ed., 2100-98) Citing, *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990) (emphasis original). In essence, the rejection boils down to an assertion that the references can be combined, not that there is any suggestion, motivation or disclosure to do so. A *prima facie* case under §103 requires far more than this.

Sufficient motivation to support the rejection requires the Examiner to demonstrate the kind of motivation which would have "*strongly motivated*" one to make a process as claimed, *Ex parte Graselli*, 231 USPQ 393, 394 (Bd. Appeals. 1983). The type of motivation required is that which would have "*impelled*" one to do so, *In re Levengood*, 28 USPQ2d at 1302, and the type of suggestion required is one that demonstrates the selection and combination "*should*" be made, *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. Appeals. 1964).

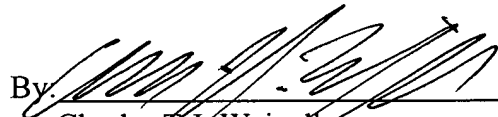
In comparison to these requirements, the Examiner's explanation of the motivation supporting the combination underlying the rejection is clearly insufficient. The references should not be considered in light of the objectives achieved by the Applicants' invention. *In re Ochiai*, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995) ("reliance on *per se* rules of obviousness is legally incorrect and must cease."); and see MPEP §2116.01 at 2100-45 (Seventh

Edition, Rev. 1, Feb. 2000). Unfounded manipulations of the reagent system disclosed in Kim, using the disclosure of Inami, apart from indicating the incompatibility of the respective systems, do not provide the factual grounds necessary for supporting the rejection. *Ex Parte Porter*, 25 USPQ2d 1141, 1147 (BPAI 1992).

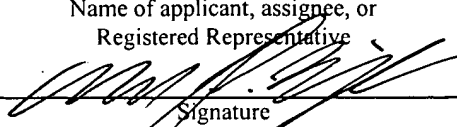
In sum, the Examiner has not adduced factual support demonstrating the requisite motivation for the combination of references advanced against Applicants claims. In addition, the citations fail to account for all the Applicants' claim limitations and lack any disclosure motivating their combination. The Examiner has not met her burden of demonstrating a *prima facie* case of obviousness, therefore, the rejection should be withdrawn.

In view of the foregoing, favorable action on the merits, and allowance of all claims, respectfully is solicited.

Respectfully submitted,

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